Identification of *IL18RAP/IL18R1* and *IL12B* as Leprosy Risk Genes Demonstrates Shared Pathogenesis between Inflammation and Infectious Diseases

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Of eight leprosy susceptibility loci identified by genome-wide association studies, five have been implicated in Crohn disease, suggesting a common genetic fingerprint between leprosy and inflammatory bowel disease (IBD). Here, we conducted a multiple-stage genetic association study of 133 IBD susceptibility loci in multiple leprosy samples (totaling 4,971 leprosy cases and 5,503 controls) from a Chinese population and discovered two associations at rs2058660 on 2q12.1 ($p = 4.57 \times 10^{-19}$; odds ratio [OR] = 1.30) and rs6871626 on 5q33.3 ($p = 3.95 \times 10^{-18}$; OR = 0.75), implicating *IL18RAP/IL18R1* and *IL12B* as susceptibility genes for leprosy. Our study reveals the important role of IL12/IL18-mediated transcriptional regulation of IFN-γ production in leprosy, and together with previous findings, it demonstrates the shared genetic susceptibility between infectious and inflammatory diseases.

Genome-wide association studies (GWASs) have offered a powerful and unbiased approach for the identification of susceptibility genes for complex diseases. As of September 2011, a total of 1,617 susceptibility loci have been identified in 249 complex traits (see Web Resources for the Catalog of Published GWASs). The enormous progress of GWASs has led to the revelation of biological connections between some clinically unrelated diseases through the identification of shared risk variants; such connections include associations between *IL23R* (MIM 607562) variants and leprosy (MIM 609888),[1] Crohn disease (CD [MIM 266600]),[2] ulcerative colitis (UC [MIM 266600]),[3] psoriasis (MIM 177900),[4] and ankylosing spondylitis (AS [MIM 106300]),[5] as well as the association between *PTPN2* (MIM 176887) variants and CD[2] and type 1 diabetes (IDDM [MIM 222100]).[6]

Of the eight leprosy susceptibility loci identified by GWASs,[1,7] variants of *NOD2* (16q12 [MIM 605956]), *TNFSF15* (9q32 [MIM 604052]), *LRRK2* (12q12[MIM 609007]), *IL23R* (1p31.3), and *LACC1/CCDC122* (13q14.11 [MIM 613409 and 613408]) have also been reported to be associated with CD and UC, suggesting a strong biological link among the genetic susceptibilities of these diseases.

Both CD and UC belong to inflammatory bowel disease (IBD [MIM 266600]), a chronic disorder affecting the intestinal mucosa. Recent GWAS analyses of CD and UC have corroborated that nearly one-third of their susceptibility loci are shared.[8] Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* and affects both the skin and the peripheral nerves. Although leprosy and CD are distinct clinical entities, they both belong to chronic inflammatory diseases, and there is some suggestive evidence that they share pathogenic mechanisms. For example, the formation of granuloma is an important clinical hallmark of both leprosy and CD. In addition, it has also been suggested that the development of CD, at least in some individuals, might be triggered by mycobacterial infection.[9,10] *Mycobacterium avium* subspecies *paratuberculosis* has been cultured and identified from the intestines and blood of CD-affected individuals.[11] It has also been hypothesized that CD susceptibility genes, such as *NOD2*, might interact with mycobacterium triggers.[12] Moreover, multibacillary infection of leprosy is associated with a type 2 helper T (Th2) cell response, whereas paucibacillary infection is associated with an immune response mediated by type 1 helper T (Th1) cells.[13] The development of IBD shows a similar pattern in which tissue injury was thought to be primarily mediated by Th1 cells in CD[14] and by Th2 cells in UC.[15] We therefore hypothesized that there are additional shared

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Table 1. Summary of the Four Independent Leprosy Samples Used in the Current Study

	Cases					Controls		
	Ethnicity	Sample Size	Mean Age	Mean Age at Onset	Male/Female	Sample Size	Mean Age	Male/Female
Sample 1[a]	Han	1,504	66.22	22.96	1,251/253	1,502	65.25	1,254/248
Sample 2[b]	Han	1,154	66	23.57	934/220	2,605	57.01	1,313/1,292
Sample 3[c]	Han	1,165	62.36	32.73	846/319	648	42.09	275/373
Sample 4[d]	Chuang	334	54.76	24.68	224/110	310	45.6	195/115
	Miao	277	53.03	27.88	193/84	190	41.48	152/38
	Yizu	236	54.37	26.71	166/70	182	43.77	147/35
	other	301	56.90	26.84	212/89	66	42.18	26/40
Total		4,971	62.63	26.19	3,826/1,145	5,503	55.71	3,362/2,141

[a]Samples collected in Shandong, Anhui, and Jiangsu provinces (eastern China).
[b]Samples collected in Shandong, Anhui, and Jiangsu provinces (eastern China).
[c]Samples collected in Yunnan, Guizhou, and Fujian provinces (southern China).
[d]Samples collected in Yunnan, Guizhou, and Fujian provinces (southern China).

susceptibility loci between leprosy and IBD and searched for more leprosy susceptibility genes by carrying out a comprehensive association study of IBD susceptibility loci in multiple independent leprosy samples from a Chinese population.

We reviewed the findings from 12 CD GWASs and seven UC GWASs through the Catalog of Published GWASs and identified within 118 genes a total of 155 SNPs that showed genome-wide significant associations (p values $< 5.0 \times 10^{-8}$) with CD, UC, or both. Of the 155 SNPs, we excluded seven within the major-histocompatibility-complex region and 15 SNPs within the five known leprosy susceptibility genes (*NOD2*, *TNFSF15*, *IL23R*, *LACC1*, and *LRRK2*). After exclusion, a total of 133 SNPs, including 75 CD-associated SNPs, 54 UC-associated SNPs, and four IBD (both CD and UC)-associated SNPs, were selected for multistage association study in the four independent leprosy samples from the Chinese population.

We conducted genotyping analyses of the four leprosy samples by using the Sequenom MassArray system (San Diego, USA). In stage 1, all 133 selected SNPs were genotyped in 1,504 leprosy cases and 1,502 healthy controls from a northern Chinese Han population. Of the 119 SNPs that were successfully designed and genotyped, 19 showed suggestive association ($p < 0.05$) in stage 1 analysis and included nine CD-associated SNPs, eight UC-associated SNPs, and two IBD-associated SNPs (Table S1, available online). In stage 2, the 19 SNPs were further genotyped in an additional three independent leprosy cohorts from the Chinese population: (1) 1,154 cases and 2,605 controls from a northern Chinese Han population, (2) 1,165 cases and 648 controls from a southern Chinese Han population, and (3) 1,148 case and 748 control minorities from southern China (Table 1). The study was approved by the institutional review board at the Shandong Provincial Institute of Dermatology and Venereology, and informed consent was obtained from all individuals.

In each of the four independent leprosy cohorts, those SNPs with a call rate < 95%, a low minor allele frequency (<0.01), or a deviation from Hardy-Weinberg equilibrium ($p < 0.01$) in the controls were excluded. We adopted a Cochran-Armitage trend test to test the genotype-phenotype association in each sample, and we performed the final analysis of the combined samples by using the Cochran-Mantel-Haenszel test. Q-tests were performed for evaluating the significance of heterogeneity among individual studies, and p values < 0.05 were considered to be significant heterogeneity.

Two associations were discovered: one at rs2058660 on 2q12.1 and one at rs6871626 on 5q33.3. Both of the SNPs showed consistent association across the four independent samples without any indication of genetic heterogeneity ($p > 0.05$). In the combined samples of a total of 4,971 cases and 5,503 controls, the associations at the two SNPs suppressed the genome-wide significance (combined $p = 4.57 \times 10^{-19}$ and odds ratio [OR] = 1.30 for rs2058660; combined $p = 3.95 \times 10^{-18}$ and OR = 0.75 for rs6871626) (Table 2).

We further investigated the association evidence within the surrounding regions of the two loci by using our previously published GWAS data set.[1] To maximize the coverage of genetic variants, we imputed the GWAS data set by using the genetic-variation data from the 1000 Genomes Project (version from February 2012), which includes 1,092 individuals from Africa (246 samples), North America (181 samples), Asia (286 samples), and Europe (379 samples). Imputed genotypes with a probability < 90%, as well as SNPs with imputation certainty < 80%, a MAF < 5%, and a missing rate > 1% were excluded from further analysis. In total, there were 6,593 samples (706 individuals with leprosy and 5,587 controls subjects) and 1,987,713 SNPs that

Table 2. Summary of the Association Results for the Two Confirmed Loci in Four Independent Samples and the Combined Samples

	SNP	
	rs2058660	**rs6871626**
Chromosome	2	5
Position	103,054,449	158,826,792
Minor/major allele	T/C	A/C
Test allele[a]	T	A
Gene	*IL18RAP/IL18R1*	*IL12B*
AF[b]	0.49	0.35
Sample 1		
p	5.67×10^{-10}	2.75×10^{-5}
OR	1.41	0.77
95% CI	1.26–1.56	0.69–0.87
Sample 2		
p	7.29×10^{-7}	7.01×10^{-7}
OR	1.29	0.75
95% CI	1.17–1.42	0.67–0.84
Sample 3		
p	8.34×10^{-3}	1.59×10^{-3}
OR	1.20	0.78
95% CI	1.05–1.38	0.67–0.91
Sample 4		
p	4.52×10^{-4}	6.29×10^{-7}
OR	1.28	0.69
95% CI	1.12–1.47	0.60–0.80
All Samples Combined		
p	4.57×10^{-19}	3.95×10^{-18}
OR	1.30	0.75
95% CI	1.23–1.38	0.71–0.81
Q-test	0.35	0.58

The following abbreviations are used: AF, average allele frequency; OR, odds ratio; and CI, confidence interval.
[a]Test allele: the allele that was used for estimating the OR.
[b]AF of the test allele in the controls of the four independent samples.

passed quality control and remained in the association analysis.

We found rs2058660 to be located within a linkage-disequilibrium (LD) block of about 480 kb on 2q12.1 (Figure 1A). Besides rs2058660 ($p = 1.49 \times 10^{-3}$; OR = 1.22), additional associations ($p < 5.00 \times 10^{-3}$) were also observed at a large number of surrounding SNPs; the most significant association was at rs1916307 ($p = 7.11 \times 10^{-4}$; OR = 1.24). Conditioning on the top SNP, rs1916307, abolished the association at rs2058660, as well as associations at the surrounding SNPs ($p_{conditional} > 0.1$). In addition to the reported CD association at rs2058660, genome-wide significant associations were also reported within the regions for asthma (at rs3771166)[16] and celiac disease (MIM 212750) (at rs917997 and rs13015714).[17,18] Although asthma-associated rs3771166 ($p = 9.91 \times 10^{-1}$; OR = 1.00) did not show any evidence of association in our previous GWAS data set, the two celiac-disease-related SNPs ($p = 1.64 \times 10^{-3}$ and $p = 1.92 \times 10^{-3}$) did show association. However, these two SNPs were in strong LD with rs2058660 ($r^2 > 0.8$), and their associations were therefore not independent from the one at rs2058660. Intriguingly, we found the associations between rs2058660 and leprosy and CD to be in the direction opposite of that of the T allele, suggesting that this SNP is a risk variant for leprosy but a protective variant for CD. Our study has indicated that the susceptibility locus for leprosy on 2q12.1 is also associated with CD and celiac disease but has the opposite genetic effect (Table S2).

We found rs6871626 to be located within a small LD block of 40 kb on 5q33 (Figure 1B). Besides rs6871626, six surrounding SNPs showed stronger association with the most significant SNP at rs1422877 ($p = 2.93 \times 10^{-4}$; OR = 0.78). These six SNPs were in high LD ($r^2 > 0.8$) and were not independent from each other. Conditioning on the top SNP, rs1422877, eliminated the association at rs6871626 ($p_{conditional} = 0.49$). SNP rs6871626 was reported to be associated with UC.[3] The associations between rs6871626 and leprosy and UC were in the direction opposite of that of the C allele, suggesting that this SNP is a risk variant for leprosy but a protective allele for UC. In addition to the reported UC association at rs6871626, genome-wide significant association was also reported for CD (rs10045431 and rs6887695),[2,19] multiple sclerosis (MS [MIM 126200]) (rs10866713 and rs2546890),[20] psoriasis (rs2546890, rs3213094, and rs2082412),[4,21,22] psoriatic arthritis (PSA [MIM 607507]) (rs12188300),[23] and AS (rs6556416).[5] However, none of these previously reported SNPs showed association with leprosy ($p > 0.10$) in our previously published GWAS data set, although our power calculation indicated that our GWAS data set should provide sufficient power (>80%) to detect these associations at $p = 0.05$. Furthermore, none of these previously reported SNPs were in LD with rs6871626 ($r^2 < 0.01$), and they (except for rs12188300) were separated from rs6871626 by a strong recombination hot spot. All together, our analyses have indicated that the leprosy susceptibility locus at 5q33.3 is also involved in the development of UC but is independent from the previously published associations with CD, MS, psoriasis, PSA, and AS within the region (Table S2).

The LD region of the leprosy susceptibility locus on 2q12.1 contained five genes: *IL1RL1* (MIM 601203), *IL18RAP* (MIM 604509), *IL18R1* (MIM 604494), *SLC9A4* (MIM 600531), and *SLC9A2* (MIM 600530) (Figure 1A). *IL1RL1*, *IL18RAP*, and *IL18R1* are part of the cytokine receptor cluster on 2q12. Whereas *IL1RL1* encodes the receptor of IL33, *IL18RAP* and *IL18R1* encode the receptors of IL18. IL33 is a ligand that is selectively expressed on

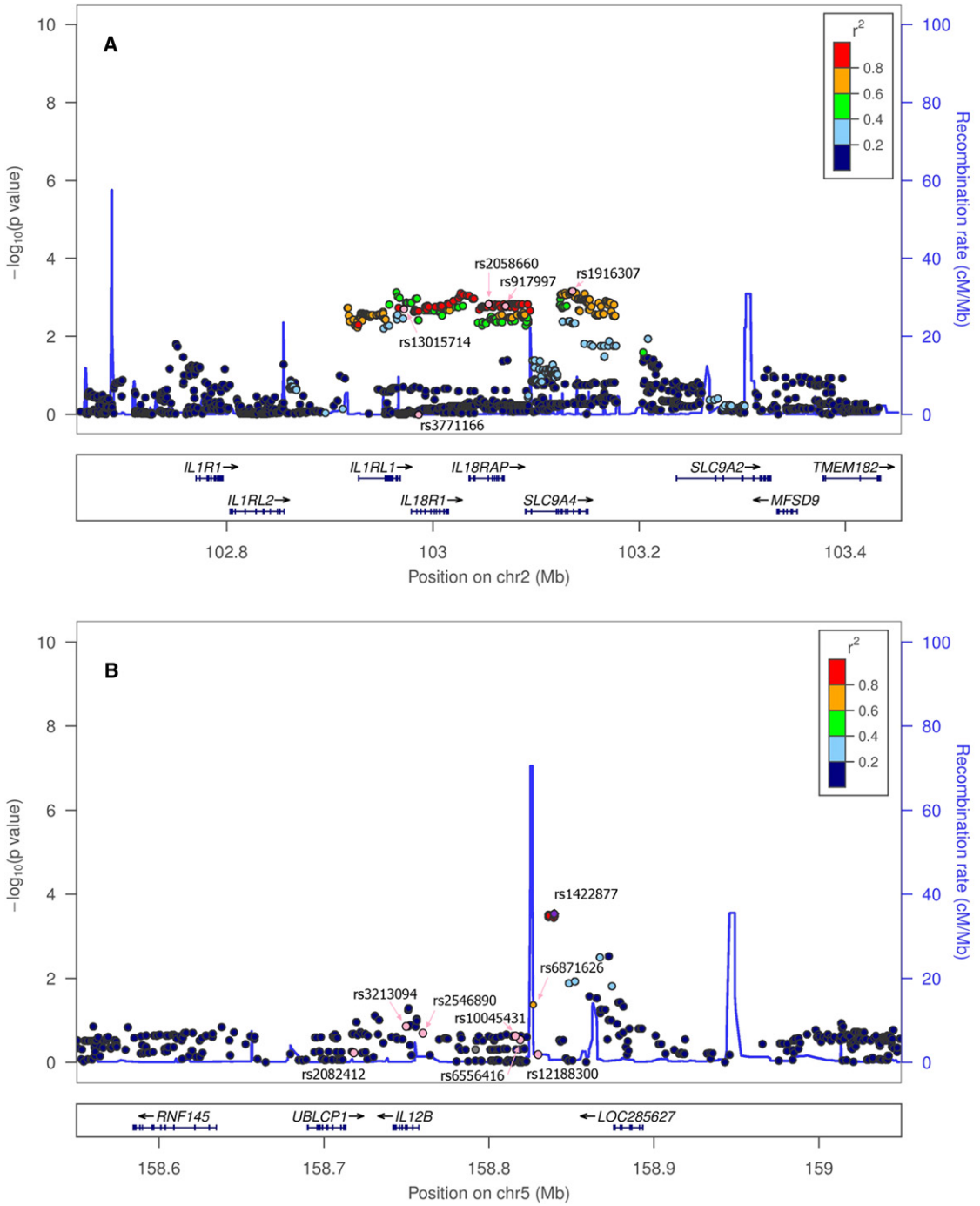

Figure 1. Regional Association Plots of rs2058660 and rs6871626
The p values of SNPs (shown as $-\log_{10}$p) (*y* axis) are plotted against their map positions (*x* axis). The color of each SNP spot reflects its r^2 with the confirmed SNP within each locus. The confirmed SNP, the top SNP, and previously reported SNPs of each locus are all in pink and are labeled with arrows. Estimated recombination rates (based on the combined CHB [Han Chinese in Beijing, China] and JPT [Japanese in Tokyo, Japan] samples from the 1000 Genomes Project) are plotted in light blue. Gene annotations were adapted from the UCSC Genome Browser (see Web Resources).
(A) rs2058660 on 2q12.1.
(B) rs6871626 on 5q33.3.

Th2 cells and mast cells and potently drives production of Th2-associatied cytokines. The signaling of different isoforms of IL1RL1 binding to IL33 plays diverse roles in the activation of nuclear factor κB (NFκB) and the subsequent inflammatory response.[24,25] Binding of IL18 to its receptors stimulates both Th1 and Th2 cytokine release and ultimately leads to the activation of NF-kB, which is a central element in the pathogenesis of leprosy.[7] It has

also been reported that IL18 can promote Th1 responses specific to *M. leprae* and can enhance IFN-γ production from natural-killer cells and Ag-stimulated T cells in response to *M. Leprae*.[26] In vitro, monocytes produce IL18 in response to *M. leprae*.[27]

The association at 5q33.3 was located within a small LD region in which only one unannotated transcript (LOC285627) could be found. However, *IL12B* (MIM 161561) is located next to the LD region and is a strong biological candidate (Figure 1B). *IL12B* encodes the p40 subunit of both heterodimeric interleukins IL12 and IL23, which play an important role in Th17-cell-mediated chronic inflammation by promoting Th17 cell maintenances and the production of proinflammatory cytokines.[28] In addition, *IL12B* has also been reported to play a role in increased susceptibility to tuberculosis (MIM 607948), although the reported association results were not conclusive and were inconsistent across different studies.[29–31] Furthermore, in vitro studies have shown that the expression of IL12B could be triggered by DNA of *M. tuberculosis* in dendritic cells through TLR9 signaling, which in turn regulates the level of IFN-γ production during infection and that IL12B is required for the generation of activated CD4 T cells and dendritic cell migration after *M. tuberculosis* infection.[32,33]

In particular, it has been demonstrated that the synergistic action of IL18 and IL12 plays an important role in IFN-γ production.[34] The synergistic action can be reflected by the induction of the IL18 receptors by IL12; this in turn leads to the induction of IL12 receptors in Th1 cells. The synergistic action can also be seen in their cooperated transcriptional regulation of IFN-γ production—different transcription factors activated by IL12 and IL18 can synergistically activate the IFN-γ promoter. Although further fine mapping and functional investigations are needed for confirming true susceptibility genes within these two loci, our findings have strongly suggested that the IL12/IL18-mediated transcriptional regulation of IFN-γ production plays an important role in the development of leprosy.

Both IL12 and IL18 pathways have been shown to be involved in the development of IBD. The IL12/IL23-mediated Th17 pathway has been shown to play an important role in the development of IBD, as well as autoimmune diseases, such as psoriasis.[28,35] In addition, previous studies have shown that the balance between IL18 and IL18-binding proteins might contribute to the pathogenesis of IBD.[36] IL18 expression is higher in the mucosa of CD-affected individuals than in uninvolved areas and normal controls.[37] Mouse models for CD show that blocking IL18 with an IL18-binding protein attenuates the intestinal inflammation.[38]

It is intriguing to see that the two susceptibility loci showed opposite associations between leprosy and IBD. In addition, of the five known shared susceptibility loci that were excluded from the current study, one SNP, rs3764147, was also analyzed in both leprosy and IBD by previous studies (Table S3). According to the published association results, the SNP showed consistent association between leprosy and IBD. Although consistent association between the two diseases supports the hypothesis that *Mycobacteria* infection might trigger or enhance the development of IBD, the opposite associations at rs2058660 and rs6871626 might suggest that historical selection against infectious diseases (such as leprosy) might prompt strong immunity whose overreaction might increase the risk of developing inflammatory diseases (such as IBD). Further studies are warranted for identifying the causal variants of these susceptibility loci through fine mapping and functional investigation and for further understanding the complex genetic basis of shared susceptibility between infectious and inflammatory diseases.

We also investigated the population-frequency differences of the reported IBD SNPs between Chinese and European populations and evaluated the power of our study to detect these previously reported IBD SNPs in our leprosy samples. We used CaTs software to calculate power by using a nominal significance of 0.05, the reported ORs in the IBD GWAS catalogue, and allele frequencies from the Chinese population. Regarding the 114 SNPs for which power analysis was performed, our study had sufficient (>80%) power to detect 35 SNPs, good (50%–80%) power to detect 20 SNPs, and insufficient (<50%) power to detect 59 SNPs (Table S4). Of these 59 SNPs, about half had a substantially lower population frequency (by at least 30%) in the Chinese population than in the European population. A much bigger study will be needed for investigating the role of these IBD SNPs in leprosy development.

In conclusion, we have discovered two susceptibility loci for leprosy by carrying out a comprehensive association study of IBD susceptibility loci in leprosy samples from a Chinese population. The discovery of the two susceptibility loci has implicated *IL18RAP/IL18R1* and *IL12B* as susceptibility genes for leprosy and highlighted the important role of IL12/IL18-mediated transcriptional regulation of IFN-γ production in the development of leprosy. Together with previous findings, our study has further demonstrated the shared genetic susceptibility basis between inflammation and infectious diseases.

Supplemental Data

Supplemental Data include four tables and can be found with this article online at http://www.cell.com/AJHG.

Acknowledgments

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Web Resources

The URLs for data presented herein are as follows:

Catalog of Published GWASs, www.genome.gov/26525384
CaTS Software, www.sph.umich.edu/csg/abecasis/CaTS/
Online Mendelian Inheritance in Man (OMIM), www.omim.org
UCSC Genome Browser, http://genome.ucsc.edu/

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